Guidance for Federal Agencies and State and Local Governments

Potassium Iodide Tablets Shelf Life Extension

DRAFT GUIDANCE

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For questions regarding this draft document contact Richard Adams at 301- 827-5849.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2003
Procedural

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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document is intended to provide guidance to Federal agencies and to state and local governments on testing to extend the shelf life of stockpiled potassium iodide (KI) tablets. The Agency has developed this document in response to several state inquiries on this topic. This guidance discusses FDA recommendations on the requisite testing for such shelf life extensions, the qualifications of laboratories suitable to conduct the tests, and issues regarding notification of holders of stockpiled KI tablets as well as end users[2] about changes to batch shelf life once testing has been successfully conducted.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For purposes of this guidance, *end users* are consumers who have purchased KI, or intermediate holders of KI such as fire departments, health departments, hospitals or other entities who store KI for use in emergencies.

II. BACKGROUND

A. Regulatory Framework

The Food and Drug Administration (FDA) has approved two new drug applications (NDAs) for Potassium Iodide Tablets, USP.[3] Both applications[4] were approved prior to 1985 and currently provide for marketing of 130-mg KI tablets over-the-counter (OTC) (i.e., without a prescription). Potassium iodide tablets manufactured by one or both holders of these NDAs have been stockpiled under controlled conditions for use in a radiation emergency.

An abbreviated new drug application[5] for Potassium Iodide Tablets, USP (65 mg), was approved on September 10, 2002.[6]

B. HHS Role in Radiological Planning and Preparedness Activities

Under 44 CFR 351, the Federal Emergency Management Agency (FEMA) has established roles and responsibilities for Federal agencies in assisting state and local governments in their radiological emergency planning and preparedness activities. The Federal agencies, including the Department of Health and Human Services (HHS), are to carry out these roles and responsibilities as members of the Federal Radiological Preparedness Coordinating Committee (FRPCC). Under § 351.23(f), HHS is directed to provide guidance to state and local governments on the use of radioprotective substances and the prophylactic use of drugs (e.g., KI tablets) to reduce the radiation dose to specific organs including dosage and projected radiation exposures at which such drugs should be used. As a part of HHS, the FDA has been providing relevant guidance to other agencies and the public on KI.

C. FDA Guidance on Safe and Effective Use of KI as a Radioprotective Agent

In November 2001, FDA provided guidance on the safe and effective use of KI tablets as an adjunct to other public health protective measures in the event that radioactive iodine is released into the environment. The guidance *Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies* updated FDA's 1982 recommendations for the use of KI tablets to reduce the risk of thyroid cancer in radiation emergencies involving the release of radioactive iodine. The recommendations in that guidance addressed KI dosage and the projected radiation exposure at which the drug should be used. In April 2002, FDA issued another guidance, *Frequently Asked Questions on Potassium Iodide (KI)*. Additional information was provided for emergency

[3] United States Pharmacopeia.

[4] NDAs 18-307 and 18-664.

[5] Application ANDA 76-350.

[6] For an up-to-date listing of all approved KI products, consult the Electronic Orange Book at www http://www.fda.gov/cder/ob/default.htm.

pediatric dosing in *Home Preparation Procedure for Emergency Administration of Potassium Iodide Tablets to Infants and Small Children*, updated on July 3, 2002.[7]

D. Shelf Life Extension of KI Tablets

A number of state and local governments maintain stockpiles of KI tablets for use in the event of a radiation emergency involving the release of radioactive iodine. Several states have asked FDA what would be required to provide confidence that stockpiled KI tablets have retained their original quality (i.e., purity and potency) after passing the expiration date.

Previously, two approaches have been used to extend the shelf life of expired drug products, the ordinary approach taken by drug manufacturers and the Department of Defense (DOD) Sponsored Shelf Life Extension Program.

1. Ordinary Shelf Life Extension

In the preferred method of shelf life extension for drug manufacturers, a manufacturer of an approved drug product may propose an extension of the expiration dating period for their product based on acceptable data from full, long-term stability studies on at least three production batches in accordance with a protocol approved in the application. The data can be reported and FDA can be notified of the extension of the expiration dating period in an annual report submitted to the NDA or ANDA if, after obtaining and analyzing the data in accordance with the protocol, the criteria set forth in the approved stability protocol are met. [8]

2. DOD-Sponsored Shelf Life Extension Program

Certain drug products have been qualified for shelf life extension through the Shelf Life Extension Program (SLEP), which is sponsored by the DOD and performed by the FDA. The SLEP is sponsored by the DOD because of the substantial savings to the government from extending the shelf life of certain antibiotics and other drug products that are stored in Federal stockpiles in large quantities under controlled conditions and are of strategic importance.

It is unlikely that any manufacturer of KI tablets would be willing to conduct testing of all of the lots of KI tablets that have already been distributed, and it would be infeasible for FDA to include KI tablets in a DOD-sponsored program. Because several states have inquired about

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[7] These guidances can be found at http:www.fda.gov/cder/guidance/index.htm; http://www.fda.gov/cder/drugprepare/KI_Q&A.htm; and http://www.fda.gov/cder/drugprepare/kiprep.htm, respectively.

[8] In June 1998, the Agency issued a draft guidance on stability testing, *Stability Testing of Drug Substances and Drug Products*. Once finalized, this guidance will represent the Agency's current thinking on this topic.

possibly testing stockpiled KI for shelf life extension, the Agency is providing this guidance on testing for such shelf life extensions of KI that is being stockpiled under controlled conditions. The Agency is also providing guidance on how to identify laboratories suitable to conduct the tests, how to notify holders of stockpiled KI tablets and end users about changes in shelf life,[9] and how to distinguish stockpiled batches with different shelf lives.

III. DISCUSSION

Studies conducted during the SLEP program on a variety of drug products have shown that shelf lives of most drug products can be extended well beyond their expiration dates, but the additional stability period for a given drug can be highly variable. It was concluded that, due to lot-to-lot variability, the stability and quality of drug products with extended expiration dates could only be assured by continual testing and systematic evaluation of each lot.[10]

A. Observations About KI Tablet Stability Based on Historical Data

Potassium Iodide Tablets, USP, is a compendial drug product that is manufactured to meet the recommended tests and specifications listed in the USP monograph. Assay and dissolution are the two specifications with potential relevance to stability, assuming identification and content uniformity testing were performed at release.[11] Stability studies over many years have confirmed that none of the components of KI tablets, including the active ingredient, has any significant potential for chemical degradation or interaction with other components or with components of the container closure system when stored per labeled directions.

To date, the only observed changes during stability testing have been the failure of some batches of KI tablets to meet the USP S_1 dissolution specification, Q=75 percent in 15 minutes. Some tablets tested required slightly longer than the specified time to achieve dissolution. Even in the case of a failure of this sort, the product would remain usable. In such cases, instructions can be provided to crush the tablets and mix them with a juice or other liquid prior to administration as suggested for emergency pediatric dosing (see Home Preparation Procedures document, cited above). In any long-term stability evaluation, appearance should be monitored as a matter of course. In the specific case of KI tablets, a yellowish discoloration would be indicative of stability problems.[6]

[9] The shelf life extension testing described in this guidance can provide confidence that only KI that has been stored in accordance with the conditions described in the labeling will retain its potency and quality for an extended period of time.

[10] "Stability Profiles of Drug Products Extended Beyond Labeled Expiration Dates," AAPS Poster Session, November 2001, Center for Drug Evaluation and Research, Office of Pharmaceutical Sciences, Division of Product Quality Research.

[11] Identification and content uniformity are performed by the quality control division of the manufacturer before the product can be released for sale.

Since pure KI is known to be very stable (as long as it is protected from moist air),[12] ongoing evaluation and testing of each batch is probably unnecessary as long as the market package remains intact and continues to be stored under controlled conditions as described in the labeling.

B. Recommended Protocol for Shelf Life Extension of KI Tablets

An example of a protocol for shelf life extension of KI tablets from a given manufacturer (manufacturer A) of stockpiled KI tablets is illustrated in the table later in this section.

We recommend that samples of three batches of KI tablets from each manufacturer be selected and stored under controlled conditions of temperature and humidity and that the samples be tested periodically for compliance with the USP assay and dissolution specifications. Each sample should consist of at least 25 tablets per test, but it would be prudent to select larger samples so that sequential testing and extensions can be performed indefinitely. Accelerated stability testing storage conditions are 40°C/75% relative humidity (R.H.). These conditions stress the product and are thought to be conservatively predictive of future stability for a period of time under room temperature conditions. Accelerated data are commonly used to establish initial expiration dates for pharmaceuticals. The expiration dates are confirmed with real time stability data. For KI tablets, results of these tests could support shelf life extensions as follows:

- If the testing results are acceptable after 3 months of storage under accelerated storage conditions, all batches of KI tablets from that manufacturer can be considered to be tentatively qualified for an additional 2 years.

Table: Example of a Protocol for Shelf Life Extension

Batch Identification	Conditions	Start date	Finish date	Tests/Specifications* per USP: Assay: 60.1-69.9 mg Diss.: 75% in 60 min. Appearance			Stations Monitored	Shelf life	Expiry
Manufacturer A	90 days accelerated.	10/1/02	12/31/02	√	√	√	0, 1, 2, 3 months	5 years (tentative)	10/04 (tentative)
"	24 months long term confirmatory	10/02	ongoing	√	√	√	0, 3, 6, 9, 12, 18, 24 months	5 years (confirmed)	10/04 (confirmed)
"	90 days accelerated	10/1/04	12/31/04	√	√	√	0, 1, 2, 3 months	7 years (tentative)	10/06 (tentative)
"	24 months long term confirmatory	10/02	ongoing	√	√	√	0, 3, 6, 9, 12, 18, 24 months	7 years (confirmed)	10/06 (confirmed)

Test	***USP Specification***
Potassium Iodide (USP method – titration)	60.1– 69.9 mg (92.5% - 107.5%) **(65 mg tablet)**
Dissolution	NLT 75% (Q) of labeled amount in 15 minutes
Appearance (visual) (Not USP)	No appreciable discoloration

[12] "Slightly deliquescent in moist air; on long exposure to air becomes yellow due to liberation of iodine, and small quantities of iodate may be formed; light and moisture accelerate the decomposition," *The Merck Index, 12th edition, 7809, Potassium Iodide*.

- We recommend that additional samples of the three batches, stored at room temperature in a warehouse or other facility, be tested at the end of 2 years from the date of initial sampling to confirm the shelf life extension tentatively qualified by the accelerated studies.
- If the product is stored under accelerated conditions for a longer period (e.g., 6 months), a longer extension of the shelf life could be tentatively qualified (e.g., for 4 years).

Testing could continue for additional shelf life extensions. We recommend that adequate records of the testing be kept even when a batch fails stability testing.

As already mentioned, in any long-term stability evaluation, we recommend that appearance be monitored. Discoloration of the tablets would provide an early indication of stability problems.

C. Identifying a Suitable Laboratory

If the decision is made to contract to have shelf life testing performed, we recommend that a suitable laboratory be identified. The testing suggested in this guidance is uncomplicated , and most laboratories should be capable of performing the tests. General laboratory GMPs are discussed in detail in *Guide to Inspections of Dosage Form Drug Manufacturer's CGMPRs*.[13] The recommended assay test is a titration. Dissolution testing and the requisite apparatus are adequately described in the USP. Since these are compendial tests, the validation of methodology is straightforward (i.e., typical parameters are listed in USP <1225>). Potassium Iodide is a very soluble drug substance and will be dissolved in the specified medium upon tablet disintegration, confirmed by measurement of the UV (ultraviolet) absorbance at the specified wavelength using a UV spectrophotometer.

D. Identification of Batches Qualified for Extension and Notification of Expired Batches

Once KI tablets from a given manufacturer have been qualified for shelf life extension by the program described above, we recommend that some provision be made to notify holders of stockpiled KI and end users as to which drug product has been qualified and what the new expiration date should be. The identification and notification procedures should be amenable to additional extensions. Potassium iodide tablets that are centrally stored can be shrink wrapped and marked with the qualified shelf life extension dates to distinguish them from other KI tablets that have different expiry dates. Each individual container need not be relabeled. End users can be notified of the extension of the expiration date using the batch identification number on each bottle.

Due to the inherent stability of KI tablets, stockpiled or distributed batches will not likely need to be replaced frequently. As noted previously, even if a batch fails the dissolution test, instructions for crushing the tablets can be provided with distributed batches.

[13] This document is available at http://www.fda.gov/ora/inspect_ref/igs/dose.html.